Allergology International. 2011;60:405-409
DOI: 10.2332/allergolint.11-RAI-0360

REVIEW ARTICLE

Pulmonary Arterial Hypertension in Connective Tissue Diseases

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ABSTRACT

Pulmonary hypertension (PH) was found to be the primary cause of death in mixed connective tissue disease (MCTD). This led to investigation of the prevalence of PH in other connective tissue diseases (CTD). In 1998, the Ministry of Health and Welfare's MCTD Research Committee revealed complication of PH diagnosed by physicians in 5.02% MCTD patients, 0.90% systemic lupus erythematosus patients, 2.64% systemic sclerosis patients, and 0.56% polymyositis/dermatomyositis patients. These results have been supported by a similar survey performed in North America.

As quite a few rheumatologists find right heart catheterization difficult to perform, doppler echocardiography is frequently used for screening and diagnosing PH. The MCTD Research Committee set the revised criteria for MCTD-PH, in which the threshold of estimated pulmonary arterial systolic pressure value for diagnosis of pulmonary arterial hypertension (PAH) is set at 36 mmHg, as proposed by the European Society of Cardiology. Right heart catheterization is strongly recommended for commencing the treatment. Since PH due to thromboembolism can potentially be cured surgically, lung perfusion scintigraphy should be performed for all patients diagnosed with PH.

Most CTD-PH are PAH, and since idiopathic PAH (IPAH) patients sometimes have immune disorders, treatment for IPAH may be applicable to CTD-PH. The greatest difference between the treatment strategy for CTD-PH and IPAH is the usage of corticosteroids and other immunosuppressants. The MCTD Research Committee updated its therapeutic guidelines for MCTD-PH in 2011. Validation of these guidelines is also needed.

KEY WORDS

connective tissue diseases, corticosteroid, doppler echocardiography, mixed connective tissue disease, pulmonary hypertension

CONNECTIVE TISSUE DISEASES (CTD) AND PULMONARY HYPERTENSION (PH)

CONCEPT OF CTD

CTD cause interstitial fibrinoid degeneration, and are defined as systemic, non-degenerative, non-neoplastic, non-infectious inflammatory diseases. This disease concept was proposed by Klemperer, a pathologist. He listed six diseases as falling within this concept: systemic lupus erythematosus (SLE); systemic sclerosis (SSc); polymyositis (PM)/dermatomyositis (DM); rheumatoid arthritis (RA); polyarteritis nodosa (PN); and rheumatic fever (RF). Other diseases have since also been considered to fall within this concept. The six diseases initially proposed by Klemperer are referred to as classic 'collagen diseases', while later diseases are referred to as diseases related to collagen diseases. Mixed connective tissue disease (MCTD), one of the diseases related to collagen diseases, was proposed as an independent disease classification that show mixed characteristics of two or more of SLE, SSc and PM/DM, are positive for anti-U1-RNP antibodies and show good response to treatment and good prognosis. Collagen diseases are now called as CTD or collagen vascular diseases.

RELATIONSHIP BETWEEN CTD AND PH

Analysis of the cause of death in MCTD has drawn attention to the involvement of PH in CTD. That is, PH was found to be the primary cause of death in MCTD, which had been thought to display good prognosis. This led to investigation of the prevalence of PH in

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Received 4 August 2011.

other CTD.

In 1998, the Ministry of Health and Welfare's MCTD Research Committee carried out the world's first national epidemiological survey.[1] Complications of PH were seen in 83 of 1,651 (5.02%) MCTD patients, 82 of 9,015 (0.90%) SLE patients, 100 of 3,778 (2.64%) SSc patients, and 19 of 3,349 (0.56%) PM/DM patients. These prevalence can be considered very high, since the prevalence of idiopathic pulmonary arterial hypertension (IPAH) in the general population is 1-5 per million. Patients were diagnosed with PH by physicians because they had shown clinical symptoms. On the consideration that other patients with latent PH exhibiting no clinical signs were probably present, a separate Research Committee of Ministry of Health, Labour and Welfare in 2003 investigated PH in CTD patients who were randomly selected, regardless of the presence/absence of symptoms.[2] PH was detected in 16.0% of MCTD, 9.3% of SLE and 11.4% of SSc patients, and patients with asymptomatic PH were at least as numerous as those with clinical signs of PH. This suggests that a similar investigation is needed in patients with CTD who present with no signs raising suspicion of PH. The above results generated in Japan have been supported by a similar survey performed at 50 institutions in North America.[3] That is, PH was diagnosed by the primary physician and by echocardiography, showing rates of 11.7% and 19.1% in MCTD patients and 18.9% and 27.7% in SSc patients, respectively. A World Health Organization (WHO) symposium on PH recommended annual echocardiography screening for patients with SSc-related diseases (i.e., SSc and MCTD), regardless of whether symptoms or changes in symptoms had been noted.

PATHOPHYSIOLOGY, DISEASE-TYPE CLASSIFICATION AND SEVERITY CLASSIFICATION OF PH ASSOCIATED WITH CTD (CTD-PH)

The causes of pulmonary artery pressure elevation include causes before and after the pulmonary capillaries. Cases caused before are called precapillary PH, while cases caused after are called postcapillary PH. Precapillary PH is also referred to as pulmonary arterial hypertension (PAH). The most recent PH classification system is the Dana Point classification,[4] described in 2008. This system classifies CTD-PH into the PAH category. However, cases of PH other than PAH are also seen in CTD patients, and at present the following four classifications exist on the basis of the pathogenesis:

・PAH: Caused by stenosis and/or occlusion of the lumen of the peripheral pulmonary artery; the main pathogenesis of CTD-PH.

・PH due to interstitial pulmonary lesions: Caused by the load on the right ventricle due to interstitial pulmonary lesions. In fact, pulmonary arterial pressure does not seem to rise markedly even when the interstitial pulmonary lesions are severe.

・PH due to chronic pulmonary thromboembolism: This category is divided, according to the results of lung perfusion scintigraphy, into two groups: one is chronic macro-thromboembolism that obstructs the artery larger than the segmental pulmonary artery and can be distinguished from IPAH, and the other chronic micro-thromboembolism that obstructs the artery smaller than the muscular pulmonary artery and cannot be distinguished from IPAH. This is often seen in antiphospholipid antibody syndrome, and sometimes accompanies severe PAH.

・PAH due to peripheral pulmonary artery vasculitis: Reported in cases of SLE and Takayasu's arteritis.

NATURAL HISTORY AND PROGNOSIS OF CTD-PH

The biggest difference between CTD-PH and IPAH is that, in cases where other symptoms manifest prior to PH in CTD patients, the possibility exists that PH can be observed from the time of onset and its natural history elucidated. The Ministry of Health, Labour and Welfare's MCTD Research Committee is thus applying periodic prospective echocardiographic observation of MCTD to analyze the natural history of PH. Interim results indicate that one-third of PH cases in MCTD show onset prior to diagnosis of MCTD, and that onset after diagnosis of MCTD takes place relatively early.[5] In half of those post-MCTD cases, PH showed onset within 1 year following onset of MCTD.

PH does not always worsen following onset, and a patient group with a relatively good prognosis and a group with poor prognosis have been defined. Statistical analysis using contingency table methods indicated the following factors as being associated with poor outcomes: pulmonary fibrosis; impaired pulmonary diffusing capacity; exertional retrosternal pain; left sternal border systolic murmur; fatigability; and elevated levels of muscle enzymes.[6] Multivariate analysis found associations for polyarthritis, definitive diagnosis of PH, elevated levels of muscle enzymes and SSc-related skin lesions. Prognosis was poor for patients who met the diagnostic criteria for PM/DM. The reasons for an association between myositis and poor prognosis are unclear, and further studies are warranted.

DIAGNOSIS OF CTD-PH

CTD-PH and IPAH do not show fundamental differences. However, since CTD-PH can potentially be treated with drugs such as immunosuppressants that cannot be used for IPAH, the importance of early diagnosis is obvious.

Doppler echocardiography and right heart catheterization are the most frequently used diagnostic tools for PH. As quite a few rheumatologists find right heart catheterization difficult to perform, the Ministry of Health, Labour and Welfare's MCTD Re-

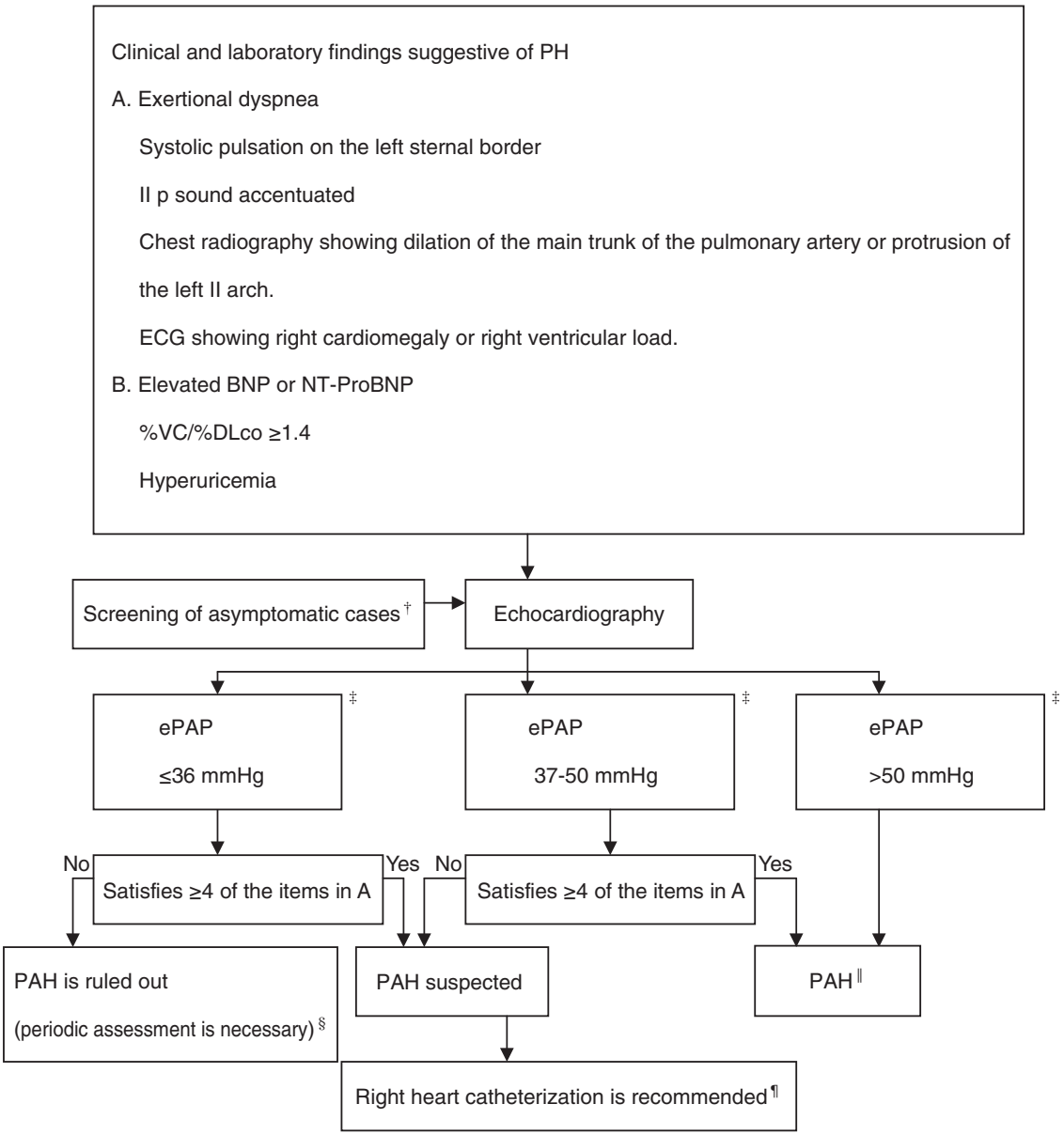

Fig. 1 Diagnostic criteria for PH in MCTD.[7] †Echocardiography should be performed on MCTD patients even when no clinical or laboratory findings suggest PH. ‡Right atrial pressure is postulated to be 5 mmHg. §In the case of recognizing the parameters suggestive of PH, other than increased estimated pulmonary artery systolic pressure, such as increased velocity of pulmonary regurgitation, shortened right ventricular ejection time to the pulmonary artery, increased diameter of right ventricle, abnormal morphology and function of the interventricular septum, increased right ventricular hypertrophy, and/or dilation of the main pulmonary artery, reassessment should be performed within at least 1 year even if the estimated pulmonary artery systolic pressure is ≤36 mmHg. ¶The course of PH should be carefully monitored in cases where right heart catheterization cannot be performed. Even when therapy is not started, echocardiography should be performed after 3 months, and the patient should be reassessed. ‖For clinical classification and assessment of the severity of PH, right heart catheterization should be strongly recommended before starting treatment.
ePAP, estimated pulmonary arterial systolic pressure.

search Committee set the revised diagnostic criteria for PH in MCTD (Fig. 1).[7] The criteria was revised with the following five items as the key principles: 1) measurement of the pulmonary artery pressure is essential for PAH diagnosis; 2) right heart catheterization is not mandatory for PAH diagnosis, but is

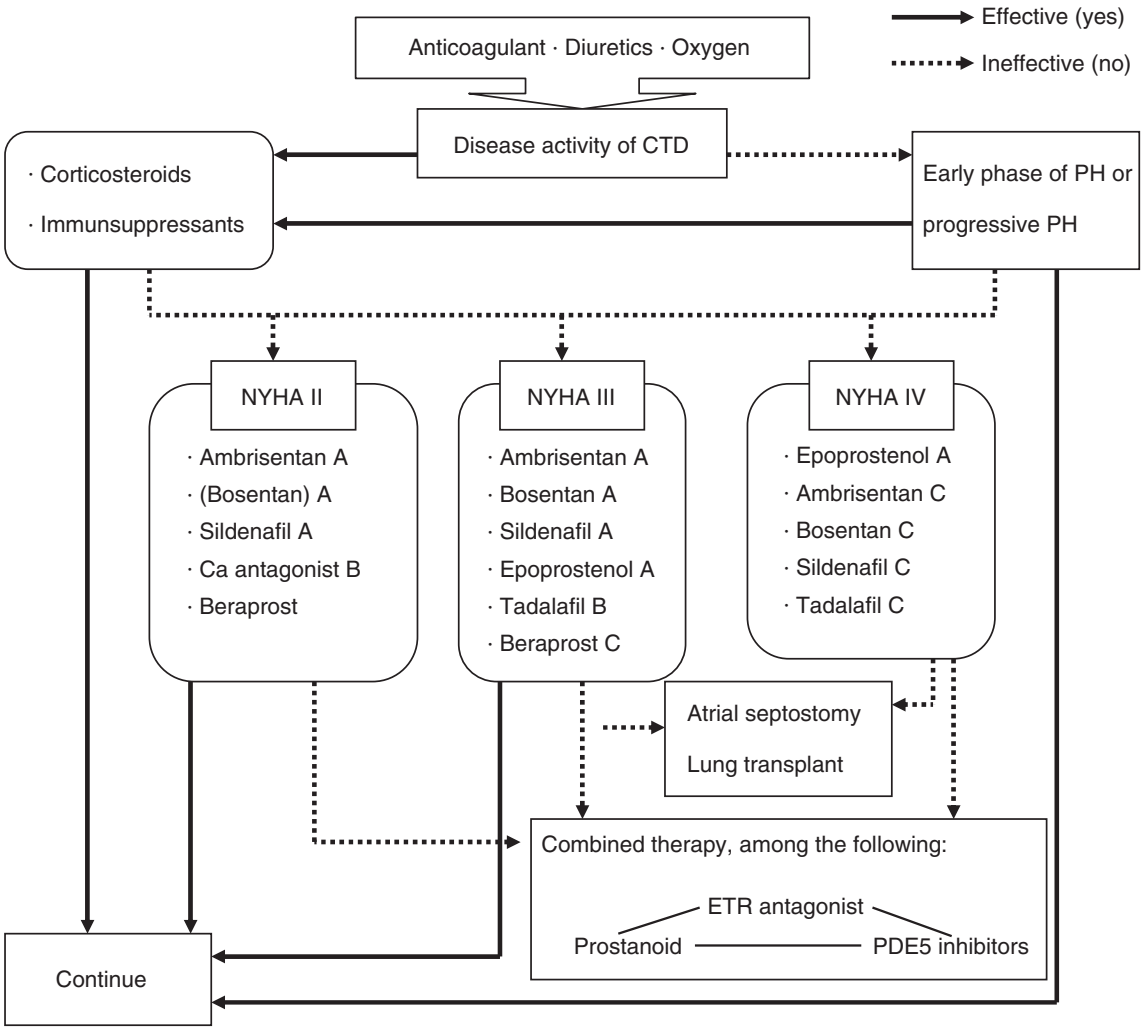

Fig. 2 Updated treatment guidelines for PH accompanying MCTD (2011).[13] Letters after drug names represent the advisability according to reference 11. Within the same advisability, the names of drugs are presented in alphabetical order. Only drugs that have been approved in Japan are shown. In Japan, the indication of bosentan is limited to NYHA class III or greater. Parentheses are thus used in the column for NYHA class II.
ETR antagonists, endothelin receptor antagonists (ambrisentan, bosentan); PDE 5 inhibitors, phosphodiesterase type 5 inhibitors (sildenafil, tadalafil); ePAP, estimated pulmonary arterial systolic pressure.

strongly recommended; 3) actual cut off values should be established for estimated pulmonary artery systolic pressure (ePAP) in the echocardiography that is necessary for PAH diagnosis; 4) clinical findings indicative of PH should also be noted; and 5) the manual is meant for diagnosis of PAH, not PH. The threshold ePAP value for diagnosis of PAH is set at 36 mmHg, as proposed by the European Society of Cardiology.[8] This diagnostic criteria may also be applicable to the diagnosis of PH accompanying other CTD, and we plan to investigate the validity of this application for MCTD.

Since PH due to thromboembolism can potentially be cured surgically, lung perfusion scintigraphy should be performed for all patients diagnosed with PH.

THERAPEUTIC APPROACH

PH due to chronic macro-thromboembolism does not respond to medical therapy. When surgery is indicated, pulmonary thromboendarterectomy should be performed. Most other cases of CTD-PH are PAH, and since IPAH patients sometimes have immune disorders, treatment for IPAH may be applicable to CTD-PH. The following is a simple summary of the treatment of this CTD-PAH that resembles IPAH:

- Rapid administration of anticoagulant;
- Administration of an effective pulmonary vasodilator to reduce load on the right heart; and
- The patient should rest and be encouraged to

eliminate factors that exacerbate PH, including smoking, infections, fever, anemia, excessive intake of salt and water, exposure to cold, and fatigue.

Three mechanisms of action are thought to underlie PH,[9] and drugs are being developed for each. The first mechanism is the endothelin pathway, mediated by endothelin as the most powerful *in vivo* vasoconstrictor. Drugs are being developed that target endothelin receptor. The second mechanism is the nitric oxide (NO) pathway. NO is a vasodilator, and substances are being developed that inhibit phosphodiesterase type 5, an enzyme that metabolizes cyclic GMP, a second messenger in the NO pathway. The third mechanism is the prostacyclin pathway. Prostacyclin (also known as prostaglandin I_2) is also a vasodilator, and analogs are being developed.

As treatment guidelines for IPAH, the American College of Chest Physicians published updated evidence-based clinical practice guidelines for medical therapy for pulmonary arterial hypertension in 2007.[10] In 2008, the WHO released updated guidelines for recommended therapeutic drugs at the Dana Point conference.[11] The greatest difference between the treatment strategy for CTD-PH and IPAH is the usage of corticosteroids and other immunosuppressants. Although there had been no comprehensive report, a retrospective study of immunosuppressive therapy in a large number of patients was published in 2006,[12] reconfirming the usefulness of this approach. The MCTD Research Committee updated its therapeutic guidelines in 2011[13] (Fig. 2). Validation of these guidelines is also needed.

CONCLUSION

The incidence of CTD-PH is high, and factors that influence prognosis have been identified. Many therapeutic agents are available, and this disease is now treatable. Physicians should always keep in mind the possibility of CTD-PH, strive to achieve early diagnosis, and administer appropriate treatment.

CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

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